

## REMARKS

This amendment responds to the office action mailed June 16, 2003. Claims 1-37 were pending in the instant Application. In the office action the PTO allowed claims 31-37, objected to claims 15-16, and 23-26 for being dependent upon a rejected claim base and rejected claims 1-14, 17-22 and 27-30 under 35 U.S.C. 103(a) over Wittwer *et al.*, in view of Brown *et al.*

With the instant amendment, claims 1-6, 18-22 and 27-30 have been canceled, without prejudice. Applicants have amended claims 7, 8, 15, 23, 25 and 26, and added new claims 38 and 39. After entry of this amendment, claims 7-17, 23-26, and 31-39 will be pending.

Applicants expressly reserve the right to pursue any canceled subject matter in one or more related, continuation, divisional or continuation-in-part application(s).

Claims 7 and 8 have been amended to independent form incorporating the limitations of claims 1 and 2. Claims 15, 23 and 25 have been amended to independent form incorporating the limitations of their base and intervening claims, as recommended by the PTO. Claim 26 has been amended to correct a minor typographical error. Support for amended claim 7 can be found in claims 1, 2 and 7 as originally filed. Support for amended claim 8 can be found in claims 1, 2 and 8 as originally filed. Support for amended claim 15 can be found in claims 1, 2, 6 and 15 as originally filed. Support for amended claim 23 can be found in claims 18, 19 and 23 as originally filed. Support for amended claim 25 can be found in claims 18, 20 and 25 as originally filed. Support for new claim 38 can be found in claims 1, 3 and 7 as originally filed. Support for amended claim 39 can be found in claims 1, 3 and 8 as originally filed. As the amendments to claims 7, 8, 15, 23, 25 and 26, and new claims 38 and 39 are fully supported by the specification and claims as originally filed, they do not constitute new matter. As the amendments to claims 7, 8, 15, 23, 25 and 26, and new claims 38 and 39 do not constitute new matter and are believed to place the claims in condition for allowance, thereby reducing the number of issues for appeal, entry thereof is respectfully requested. Further, Applicants submit that the total number of claims pending after entry of instant amendment is fewer than that pending before the issuance of the instant Office Action.

## **I. THE REJECTIONS UNDER 35 U.S.C. § 103**

Claims 1-14, 17-22 and 27-30 stand rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Wittwer *et al.*, 2001 (U.S. Patent No. 6,232,079, “Wittwer”) in view of Brown *et al.*, 2000 (U.S. Patent No. 6,143,496, “Brown”). Applicants submit that the cancellation of claims 1-6, 18-22 and 27-30 renders the rejection of these claims moot. Applicants traverse the rejection of claims 7-14 and 17 on the grounds that the references cited by the PTO are not sufficient to establish a *prima facie* case of obviousness against any of the claims.

### **A. The Legal Standard**

To reject claims in an application under 35 U.S.C. § 103, the Patent Office bears the initial burden of establishing a *prima facie* case of obviousness. *In re Bell*, 26 USPQ2d 1529, 1530 (Fed. Cir. 1993); MPEP § 2142. In the absence of establishing a proper *prima facie* case of obviousness, applicants who comply with the other statutory requirements are entitled to a patent. *In re Oetiker*, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). In order to establish *prima facie* obviousness, three basic criteria must be met.

First, the prior art must provide one of ordinary skill in the art with a suggestion or motivation to modify or combine the teachings of the references relied upon by the PTO to arrive at the claimed invention. When an obviousness determination relies on one reference, there must be suggestion or motivation to modify the teaching of the reference in the manner suggested by the PTO. *In re Grabiak*, 226 USPQ 870 (Fed. Cir. 1985). Alternatively, when an obviousness determination relies on a combination of two or more references, there must be some suggestion or motivation to combine the references. *WMS Gaming Inc. v. International Game Technology*, 51 USPQ2d 1385, 1397 (Fed. Cir. 1999). The suggestion or motivation to combine the references generally arises in the references themselves, but may also be inferred from the nature of the problem or occasionally from the knowledge of those of ordinary skill in the art. *See id.* The mere fact that references could be modified or combined does not render the resultant modification or combination obvious unless the prior art also suggests the desirability of the modification or combination. *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990); MPEP § 2143.01.

Second, the prior art must provide one of ordinary skill in the art with a reasonable expectation of success. Thus, the skilled artisan, in light of the teachings of the prior art,

must have a reasonable expectation that the modification or combination suggested by the PTO would succeed. *In re Dow*, 5 USPQ2d 1529, 1531 32 (Fed. Cir. 1988).

Third, the prior art, either alone or in combination, must teach or suggest each and every limitation of the rejected claims. *In re Gartside*, 53 USPQ2d 1769 (Fed. Cir. 2000). The teaching or suggestion to make the claimed invention, as well as the reasonable expectation of success, must come from the prior art, not Applicants' disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991). If any one of these criteria are not met, *prima facie* obviousness is not established, and Applicants are not required to show new or unanticipated results. *In re Grabiak*, 226 USPQ 870 (Fed. Cir. 1985).

**B. Wittwer and Brown, Alone or in Combination, Do Not Teach or Suggest Each and Every Element of Claims 7-14 and 17**

Applicants respectfully submit that the references cited by the PTO are not sufficient to establish a *prima facie* case of obviousness against claims 7-14 and 17 because neither Wittwer nor Brown, alone or in combination, teaches or suggests each and every element of claims 7-14 and 17. Further, Applicants respectfully submit that the references cited by the PTO are not sufficient to establish a *prima facie* case of obviousness against new claims 38 and 39 because neither Wittwer nor Brown, alone or in combination, teaches or suggests each and every element of claims 38-39.

Applicants respectfully submit that, contrary to the PTO's allegations, Applicants have not, either in previous responses, or in this response, attacked the references cited by the PTO individually. Applicants have maintained throughout, as they do here, that none of the references cited by the PTO, alone or *in combination*, teach or suggest each and every element of the pending claims.

In particular, neither Wittwer nor Brown teaches or suggests a method for absolute or relative quantification of a target nucleic acid comprising the step of determining the amplification efficiencies of the target nucleic acid and the reference or standard nucleic acid as a basis for calculation of either the original copy number or the ratio of target and reference nucleic acid. Brown does not teach *any* method of determining amplification efficiency. The PTO cites column 41, lines 44-46 of the Wittwer reference as pointing to example 16 for a method for determining amplification efficiency. Applicants submit that example 16 does not teach or suggest a method of determining amplification efficiency.

Instead, in example 16, column 41, and figure 44, Wittwer discloses that the area under the melting peak is indicative of the *quantity* of nucleic acid present in the sample. Applicants submit that while a rough estimation of amplification efficiency might be estimated from the quantity of nucleic acid present in the sample obtained by integrating the melting peak data, this is different from determining a non-linear continuously differential function as a basis for the calculation of amplification efficiency which is *subsequently* used for either absolute or relative quantification of the target nucleic acid.

Further, the PTO contends that Wittwer (figures 15-17, 20-21, and 42, and column 33, line 10-column 34, line 52) teaches determination of a non-linear continuously differential function of a logarithm of copy number of target nucleic acid used for amplification as a function of the cycle number in which a threshold value is achieved. Applicants respectfully submit that this is incorrect. As pointed out in the response filed to the Office Action dated January 21, 2003, not only does Wittwer *not* teach setting a threshold value, but, by teaching the disadvantages of choosing “a ‘threshold value’ of the signal and then [using] the cycle number when the standard or unknown crosses that threshold,” it in fact *teaches away* from setting threshold values and using the cycle number when the standard or unknown crosses that threshold (column 33, lines 22-29).

Applicants submit that neither Wittwer nor Brown, alone or *in combination*, teach or suggest a method for quantification of a target nucleic acid that takes into consideration a pre-determined amplification efficiency. Since neither Wittwer nor Brown, alone or *in combination*, teaches or suggests, for instance, a method of determining amplification efficiency as a function of the amount of nucleic acid based on the determination of a cycle number at which a threshold is exceeded, as recited in amended claims 7-14, 17 and new claims 38-39, the PTO’s combination of references fails to teach or suggest each and every element of claims 7-14 and 38-39. The combination of references is therefore not sufficient to establish a *prima facie* case of obviousness against claims 7-14, 17 and new claims 38-39.

Moreover, in contrast to the PTO’s assertion, neither Wittwer nor Brown teaches or suggests the use of a calibrator sample. Applicants respectfully submit that the PTO appears to have used phrases and concepts taught only in the instant specification to characterize the cited references. For example, the PTO alleges that Column 10, lines 30-50 of Brown “clearly teaches a reference nucleic acid standardized with a calibrator sample and the calculation of the ratio of target nucleic acid to reference nucleic acid” (Office Action, p. 9).

The cited lines of Brown, however, do not even contain the words “ratio,” “reference,” or “standardized,” and the entire Brown reference fails to even mention a calibrator sample. Applicants respectfully submit that these phrases are used only in the instant specification to explain the concept of a calibrator sample and the advantages of using one.

Further, the PTO contends that example 16 and column 8, line 40, to column 9, line 19, of Wittwer allegedly “clearly teaches” a “calibrator sample” and the “determination of the ratio of the two quotients as a measure for the original amount of target nucleic acid contained in the sample.” Again, Applicants respectfully submit that that these phrases and concepts are taught only in the instant specification and that the words “calibrator” and “quotient” are not found *anywhere* in Wittwer. Applicants submit that although example 16 might teach the quantification of a nucleic acid, it does not teach the use of a calibrator sample or the determination of a ratio of quotients. Further, the section of Wittwer from column 8, line 40, to column 9, line 19, has nothing whatsoever to do with a calibrator sample or a ratio of quotients. Instead, the cited section teaches detecting a difference at a selected locus in a first nucleic acid as compared to a second nucleic acid (*see* column 8, lines 40-42 and column 9, lines 16-19).

As disclosed in the instant specification, and known to one of ordinary skill in the art, a calibrator sample is used to compensate for or eliminate systemic errors that are due to differences in the detection sensitivity of the target nucleic acid and the reference nucleic acid, but are *not* due to differences in either amplification efficiency or in different target or reference nucleic acid concentration. Neither Wittwer nor Brown, alone or in any combination, teaches or suggests the use of such a calibrator sample.

Since neither Wittwer nor Brown, alone or in any combination, teaches or suggests, for instance, the determination of cycle numbers at which signal thresholds are exceeded for dilutions of the target nucleic acid and the reference nucleic acid or the use of a calibrator sample as recited in claims 9 and 10, the PTO’s combination of references fails to teach or suggest each and every element of independent claims 9 and 10. Since claims 11-14 and 17 ultimately depend from claims 9 and/or 10, the combination of references is also not sufficient to establish a *prima facie* case of obviousness against claims 11-14 and 17.

In view of the foregoing, Applicants respectfully request that the rejection of claims 7-14 and 17 under 35 U.S.C. § 103(a) be withdrawn.

### CONCLUSION

Applicants respectfully contend that all grounds for rejection have been overcome and/or obviated by the amendments and remarks set forth herein, and that claims 7-17, 23-26, and 31-39 are in condition for allowance. Accordingly, the PTO is respectfully solicited to allow claims 7-17, 23-26, and 31-39. The Examiner is invited to call the undersigned attorney if a telephone call could help resolve any remaining issues.

Pursuant to 37 CFR § 1.136(a)(3), the Commissioner is authorized to charge all required fees, fees under 37 CFR § 1.17 and all required extension of time fees, or credit any overpayment, to Pennie & Edmonds, LLP U.S. Deposit Account No. 16-1150 (order no. 1803-326-999).

Respectfully submitted,

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